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REVIEW ARTICLE

# *Bothrops moojeni* venom and its components – an overview

Fernanda D'Amélio[1, 2*], Hugo Vigerelli[1,2,3], Álvaro Rossan de Brandão Prieto da Silva[1] and Irina Kerkis[1,3*]

[1]Laboratory of Genetics, Butantan Institute, São Paulo, SP, Brazil

[2]The Postgraduate Program in Toxinology, Butantan Institute, São Paulo, SP, Brazil

[3]Centre of Excellence in New Target Discovery (CENTD), Butantan Institute, São Paulo, SP, Brazil

***Correspondence to:** Irina Kerkis, Email: irina.kerkis@butantan.gov.br and Fernanda D'Amélio, Email: fernanda.damelio@butantan.gov.br

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## ABSTRACT

Belonging to the Viperidae family, *Bothrops moojeni* are widely distributed in South America, tropical savanna ecoregion (Cerrado) of Argentina, Bolivia, Brazil, and Paraguay with medical importance in Brazil. Accidents caused by this species have a rapid local action with the development of tissue inflammation, causing erythema, pain, and increased clotting time, which can culminate in gangrene or tissue necrosis. *Bothrops moojeni* venom has a rich composition that remains underexplored, which is of utmost importance, both for elucidating the envenoming process and the vast library of new bioactive molecules kind of venom can offer. This review aims to analyze which components of the venom have already been characterized towards its structure and biological effect and highlight the pharmacological and biotechnological potential of this venom. Although snake venoms have been studied for their toxic effects for generations, innovative studies address their components as tools for discovering new therapeutic targets and new molecules with pharmacological and biotechnological potential.

**KEYWORDS:** *Bothrops moojeni*, components, Snake venom, metalloprotease, serinoprotease, phospholipase, L-amine oxidase acid

## INTRODUCTION

It is estimated that approximately 5.4 million people are bitten by snakes every year, with up to 2.7 million envenomings, causing more than 100 thousand deaths globally (World Health, 2016). The venom is composed by several different molecules, such as proteins, peptides, enzymes, toxins, biogenic amines, lipids and inorganic cations (León et al, 2011), snake venom inoculation in an organism triggers two simultaneous processes: the development of toxic effects induced by venom`s toxins, and stimulation of the innate and adaptive immune system response, which acts to neutralize and remove venom`s proteins. When the venom is capable of generating local and systemic damage, exceeding the animal's ability to assimilate and affect the response to aggression, and envenomation is developed (León et al, 2011).

Among the major families of snakes, the Viperidae family is represented by over 350 venomous species (Uetz et al, 2020). Unlike many other snakes, the movable jawbone and a sophisticated apparatus for venom injection characterize this family, which provides the high mortality and morbidity of these snakes to its prey (Theakston and Warrell, 1995).

Occurring at all taxonomic levels of these animals, the variation in venom composition confers a variability in function and a significant influence on the treatment of venomous accident victims, besides the development of antivenoms (Theakston and Warrell, 1995).

Bothrops moojeni (Hoge, 1966) (Figure 1A) belongs to the Viperidae family and are widely distributed in South America tropical savanna ecoregion (Cerrado) of Argentina, Bolivia, Brazil, and Paraguay, being especially abundant in Brazil (Borges and Araújo, 1998), in the central, northern and southeastern regions (Figure 1B) (Nogueira et al, 2003), where are account for about 90% of snakebite accidents (Kouyoumdjian and Polizelli, 1988). With medical importance, accidents caused by snakes of this species have a rapid local action with the development of tissue inflammation, causing erythema, pain, and increased clotting time, which can culminate in gangrene or tissue necrosis, when treatment is not administered (Kouyoumdjian and Polizelli, 1988, 1989). Systemic effects involving changes in blood coagulation and cardiovascular system can lead to, in more severe cases, hypovolemic shock and acute renal failure (Sampaio, 2009; Nascimento et al, 2010).

Although snake venoms have been studied for its toxic effects for generations, innovative studies are addressing the use of its components as tools for the discovery of new therapeutic targets and new molecules with pharmacological and biotechnological potential. *Bothrops moojeni*, although it is one of the snakes of great epidemiological importance in Brazil, has a range of molecules in its venom that can be better studied and applied in different biological models. Therefore, this study aimed to analyze which components of the venom have already been characterized by its structure and biological effect, as well as highlight the pharmacological and biotechnological potential of this venom.

## METHODOLOGY

The bibliographic survey was carried out in 2020, based on the already characterized components of *Bothrops moojeni* venom. Database search was performed using PubMed and Uniprot, searching for the terms: *Bothrops moojeni* (Lance-headed viper) (Caissaca) [98334]" (keyword: toxin OR annotation :( type:"tissue specificity" venom)) AND reviewed: yes; "*Bothrops moojeni* and components," "*Bothrops moojeni* venom," "Characterization of *Bothrops moojeni* Components." As selection criteria, all articles containing chemical characterization and function of components of the snake venom were used.

## RESULTS

## VENOM COMPONENTS

Snake venoms have immunogenic components such as proteins, which make up over 98% of its dry weight, including toxins that can induce severe toxic effects and those that have no toxic effects. They also have non-immunogenic components such as amino acids, nucleotides, carbohydrates, lipids, and biogenic amines, representing less than 2% of the dry weight (León et al, 2011).

### Snake venom metalloproteases (SVMPs)

These molecules constitute from 30 to 60% of Viperidae family snakes venom (Calvete Chornet et al, 2009) and are classified into three groups according to the domain they present in their molecular composition: **P-I SVMPs** - Have a molecular mass of 20-30kDa, composed of a single zinc ion-binding metalloprotease domain, which is a catalytic domain: **P-II SVMPs** - Have a molecular mass of 30-60kDa, composed of a disintegrating domain in addition to the catalytic domain: **P-III SVMPs** - Have a molecular mass of 50-70kDa, composed of a disintegrin-like domain and

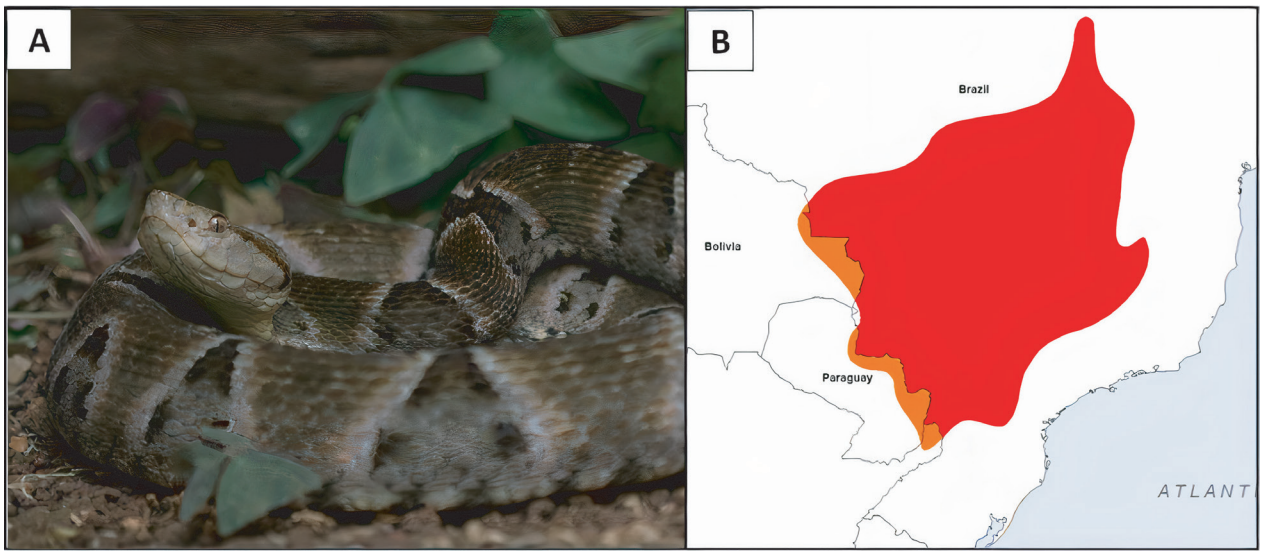


**Figure 1:** Bothrops moojeni snake and its distribution in South America. **A.** Photo taken by Sávio Stefanini Sant`Anna, from Laboratory of Herpetology, Institute Butantan. **B.** Geographic distribution of the Bothrops moojeni snake in Brazil. Source: World Health Organization, available at: http://apps.who.int/bloodproducts/snakeantivenoms/database/Images/SnakesDistribution/Large/map_Bothrops_moojeni.pdf. Accessed on 12/04/2018.

cysteine-rich domain. Some have a quaternary structure, a typical subunit of P-III SVMPs, which is linked via a disulfide bond to a smaller lectin type C subunit (Fox and Serrano, 2009).

SVMPs of all classes affect hemostasis by inducing defibrinogenesis, activating coagulation X factor, and prothrombin (Moura-Da-Silva et al, 2009), resulting in stimulation of fibrinogenolytic action (Stöcker and Bode, 1995; Swenson and Markland Jr, 2005). They also actively participate in extracellular matrix degradation, thus promoting an inflammatory reaction (Teixeira et al, 2005). SVMPs can present a potential use as a thrombolytic agent. A fribolase isolated from Agkistrodon contortrix (Ahmed et al, 1990), for example, has shown a potent fibrinolytic activity, and "Alfimeprase," its recombinant form, was used for the treatment of abnormal blood clot formation, besides to cause thrombolysis in acute limb ischemia effectively. Although its pharmacological effect has secured approval on Phase I and II clinical trials, this drug was withdrawn on Phase III, due the patients were not able to meet peripheral arterial occlusion (Deitcher and Toombs, 2005).

On the other hand, Moojenin, an SVMPs isolated from Bothrops moojeni (de Morais et al, 2012), with an anticoagulant application, is already a drug in clinical use (named Defribase) for the treatment of ischemia caused by vascular occlusive diseases, peripheral and microcirculation dysfunctions, and acute cerebral infarction. The capacity to decrease in fibrinogen levels, anticoagulation, and inhibition of thrombogenesis is among the pharmacological activities of this SVMPs (Wang et al, 2001). All Bothrops moojeni venom characterized metalloproteases, classification, and experimental models, are exemplified in Table 1.

**Serineproteases**

Serineproteases constitute 10 to 30% of Viperid venom. They characterized by the molecular mass of 25-70kDa and conservation of a catalytic triad (Ser, His, and Asp), as well as by the presence of many disulfide bonds (Braud et al, 2000). Thrombin-like serineproteases can cleave fibrinopeptide A or B, which are derived from fibrinogen that causes the formation of degraded microcoagles by the fibrinolytic system, contributing to the defibrinogenation process (Markland, 1998; Swenson and Markland Jr, 2005). Batroxobin a snake venom enzyme with venombin A activity, also known as reptilase. This thrombin-like serineprotease has a specific action on fibrinogen (Schunk and Macallum, 2005). Its venom purification is used therapeutically for defibrinogenesis in patients suffering from thrombotic diseases. Repeated administration may cause antibody synthesis, which response to decreased therapeutic potential and enzyme activity (Lochnit and Geyer, 1995). Serineproteases, which are kallikrein-like enzymes (Komori et al, 1988), generate bradykinin (plasma peptide with vasodilatory and inflammatory function) and contribute to hypotension (Iwanaga et al, 1976; Komori et al, 1988).

**Phospholipases**

With a molecular mass of 14-18kDa, it can be found in multimeric structures, including dimeric, trimeric, and pentamer molecules (Fraenkel-Conrat and Singer, 1956). They constitute 5 to 45% of the venom, varying by species (Calvete Chornet et al, 2009). Viperid venom presents PLA group homologs, in which ASP49 is replaced by Lys or other residues, this type of substitution nullifies the catalytic activity, even though they present their toxicity (Lomonte et al, 2009; Santos-Filho et al, 2008).

In envenomation, phospholipase plays many roles due to its ability to bind to different tissue targets (Kini, 2003), inducing neurotoxicity, myotoxicity, hypotension, anticoagulation, inhibition of platelet aggregation and hemolysis (Kuruppu et al, 2008). In some cases, it also can hydrolyze phospholipids, and some of the effects are independent of catalysis and result in the interaction of phospholipases with plasma membrane receptors (Kini, 2003).

**L- amino acid oxidases**

L-amino acid oxidases are flavoenzymes that catalyze oxidative stereospecific deamination of L-amino acids corresponding to alpha-keto acid, with the production of hydrogen peroxide and ammonia via the intermediate amino acid pathway. These enzymes are present in different organisms, such as bacteria, fungi, green algae, and snake venoms, and are used as a source for nitrogen synthesis (Fry et al, 2006;

**Table 1:** *Bothrops moojeni* venom characterized metalloproteases, classification, and experimental models.

| **Metalloprotease** | | | | | | |
|---|---|---|---|---|---|---|
| **ID Uniprot** | **Molecule Name** | **Class** | **Function** | **Experimental model** | | **Reference** |
| | MPB | P-II | Low blood clotting activity | - | *In vitro* (collagen) | Serrano et al, 1993 |
| - | BthMP | P-I (suggested) | Proteolytic activity | *In vivo* (Swiss mice) | - | Gomes et al, 2009 |
| - | FIBMP-I | P-I B | Fibrinolytic activity | - | *In vitro* (fibrinogen) | Torres et al, 2012 |
| P0DKR0 | Moojenin | P-III | Fibrinogelitic, autolysis, and proteolysis | *In vivo* (Swiss mice) | - | de Morais et al, 2012 |
| P85314 | BmooMPα-I | P-IB | Fibrinogelitic, Fibrinolytic | - | *In vitro* (kininogen) | Okamoto et al, 2014 |
| - | Moojenactivase (MooA) | P-III | Disseminated i ntravascular coagulation | *In vivo* (Wis-tar) | *In vitro* (PBMC) | Sartim et al, 2016 |

**Table 2:** *Bothrops moojeni* venom characterized phospholipases, classification, and experimental models.

| Phospholipase | | | | | |
|---|---|---|---|---|---|
| **ID uniprot** | **Molecule Name** | **Class** | **Function** | **Experimental model** | **Reference** |
| - | Moojeni protease A | PLA | Proteolytic activity | *In vitro* (anti-body) | Assakura and Mandelbaum, 1990 |
| P82114 | MjTX-II | Lys19 PLA2 | Myonecrosis | *In vivo* | Stábeli et al, 2006 |
| A0A1S5XW05 | BmooTX-I | Asp49 (PLA2) | Indirect hemolytic activity, myotoxic, prostaglandin induction, platelet inhibition. | In *vivo* (Swiss mice) | Santos-Filho et al, 2008 |
| G3DT18 | BmooPLA2 | Lys49 | Myotoxic action, Platelet inhibition | In vivo (Swiss mice) | Silveira et al, 2013 |
| P82114 | MjTX-I | Lys19 PLA2 | Edema | *In vivo* | Salvador et al, 2018 |

Gutiérrez et al, 2006). svLAAOs are related to inhibition of platelet aggregation induction and vascular endothelial cell apoptosis. These events contribute to the prolongation of vessel bleeding and vascular wall damage (Gutiérrez et al, 2006; Hill and Mackessy, 2000; Stábeli et al, 2007).

***Bothrops moojeni* venom L-aminoacid oxidases**

L-AAO - Catalysis and oxidative deamination are of L-amino acids corresponding to α-ketoacid, hydrogen peroxide, and ammonia, and features activity against *Leishmania* (Stábeli et al, 2007; Tempone et al, 2014).

**Glycoproteins**

Lectins are polyvalent carbohydrate-binding proteins, structurally diverse, but capable of binding to oligosaccharides with considerable specificity. They have many biological activities, such as the ability to agglutinate erythrocytes, lymphocytes, bacteria, fungi, and cancer cells (Fry et al, 2006). Lectin specificity has been used to detect cell surface sugars, enzymes, immunoglobulins, tumorigenic cells, and liposome-conjugated lectins, as well as drug loading. Many lectins have been isolated from snake venoms and are described as calcium-dependent beta-galactosidase linker proteins (Fox and Serrano, 2008), showing intermediate properties between CDR type C and S (Chippaux, 1998). They induce red cell agglutination (Gutiérrez et al, 2006), stimulate human platelet aggregation (Gutiérrez et al, 2010), and are mitogenic to T lymphocytes (Kasturiratne et al, 2008), and cytotoxic to some cancerous, renal and pancreatic cells (Mehta and Sashindran, 2002).

***Bothrops moojeni* venom Glycoproteins**

**MBool -** Characterized as calcium-dependent galactoside protein binder. There is a high level of structural homology of BMooL and other venom lectins from other snakes, the determination of molecular structure is interesting for knowledge of the function and chemical structure. Shows haemagglutination activity and does not cause inhibition of platelet aggregation when the process is induced by collagen (Kassab et al, 2001). **BmjMIP -** Mycotoxin Inhibitor Protein (BmjMIP) is an oligomeric glycoprotein, shows a high similarity with other phospholipase A2 inhibitors, in which the carbohydrate recognition domain (CRD) and glycosylation site (Asn103) are conserved. Shows inhibitory action against Bothrops' basic and acidic PLA2s (Soares et al, 2003).

**Peptides**

Bradykinin-Potentiating Peptides (BPPs) have been found in many snake venoms in various Bothrops species (Cintra et al, 1990; Murayama et al, 1997; Ferreira et al, 1998; Hayashi et al, 2003; Ianzer et al, 2004; Hayashi and Camargo, 2005). The article's methodology is a screening of BPPs of *Bothrops moojeni* crude venom, based on the conserved Pro-Pro and C-Terminal sites, and post-transcriptional modifications of pGlu and N-terminal. It was characterized using MALDI-TOF-MS combined with Edman degradation techniques (Menin et al, 2008).

About 43 different compounds were detected in this venom by this shotgun analysis. A total of 134 components were detected, 33% by ESI-MS, 72% by LC-ESI-MS, and 23% by MALD-TOF-MS. Nine peptides could be detected between these components and seven compounds related to BPP. Twenty-three pyroglutamate peptides/BPPs obtained by ESI-MS/MS, from the crude venom components, were sequenced (Menin et al, 2008).

## TOXINS IN IMMUNITY

**Non-specific initial immune response associated with inflammation**

Inoculation of snake venom in mammalian tissues generates inflammation and is a non-specific defense mechanism that constitutes a general and prompt response to external agents. In the case of viperid venoms, this process is characterized by prominent edema, inflammatory cell infiltrate, and pain (Teixeira et al, 2009). This inflammatory response is regulated by several mediator classes, such as eicosanoids, nitric oxide, cytokines, matrix metalloproteinases, kinins, and complement (Farsky et al, 2005; Teixeira et al, 2009), may cause coagulopathy, neurotoxicity, myotoxicity, hypotension, and tissue necrosis (León et al, 2011).

***BOTHROPS***

Venom components with a molecular mass greater than 30kDa, such as P-II and P-III SVMPs, L amino acid oxidase, and Serino proteases, are recognized and immunoprecipitated by antivenom antibodies. Venom components with a molecular mass of less than 20kDa, such as PLA2, are immuno-depleted only for partial activity (Judge et al,

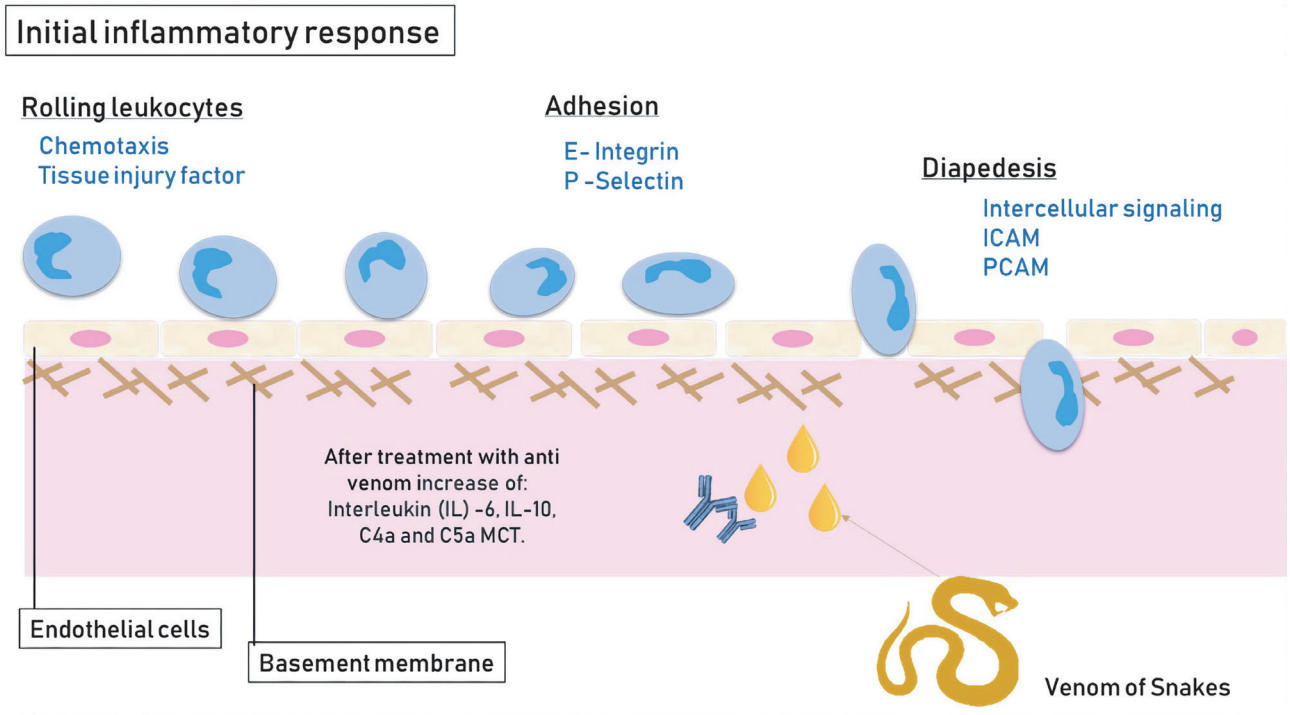


**Figure 2:** Initial immune response in snakebite accident representation.

2006; Gutiérrez et al, 2010). Venom components with less than 5kDa, such as disintegrins and BPPs, do not produce a detectable antibody response.

**Anaphylaxis in response to *Bothrops* venom**

Anaphylaxis is characterized as a mediator of immunity or non-mediator, IgE-dependent or not (Lalloo and Theakston, 2003). IgE-dependent anaphylaxis occurs as a result of allergen exposure, resulting in between a specific allergy link and IgE binding to the surface of mast cells with subsequent degranulation and release of histamine and tryptase by the mast cell (mast cell-released serine protease/MCT), for this to occur, exposure to the allergen is required (Lalloo and Theakston, 2003).

**Moojeni protease A**

Moojeni protease A causes proteolysis of rat and human type G (IgG) immunoglobulins (Assakura et al, 1985). The enzyme is not activated by triol, in contrast to previously known enzymes, directly generating IgG Fab fragments. Human and rat IgG are protease digested by the presence of an IgG L chain, and the disappearance of an H chain indicating that the protease is cleaving peptide bonds in the heavy chains near the disulfide bonds of the heavy IgG chains (Assakura and Mandelbaum, 1990).

## Moojenactivase

MooA stimulates inflammatory cytokines production, such as TNF-alpha, IL-8, and MCP-1 chemokines. All inflammatory mediators have been described in the expression of TF leukocytes (Herbert et al, 1992; Sardo et al, 2008; Schecter et al, 1997), showing that MooA may have immunomodulatory ability (Chen et al, 2008; Kim et al, 2012; Nieuwenhuizen et al, 2013; Sartim et al, 2016).

***Bothrops moojeni* crude venom: General considerations**

A study showed an important interspecies variation in *Bothrops moojeni* venom, using biochemistry techniques, such as electrophoresis gels and proteolytic potential assays, as also *in vivo* experiments such as edema assay, among others. This important study reinforces the variation among the venom molecules, froman individual to the individual perspective, also in comparison between species. Contributing to the analysis of the composition of the venom and interpretation of data and biological effects in other systems (Aguiar et al, 2019).

In addition, another study performed the *Bothrops moojeni* venom gland transcriptome, identifying: Metalloproteases (PI-SVMPs / PII-SVMP / PIII-SVMP); Serine proteases; Phospholipases; Phosphodiesterases; C-type lectins; L-amino acid oxidases; Bradykinin-potentiating; Cysteine-rich secretory proteins, and 3-Finger toxins. This finding was extremely important for the characterization and expansion of knowledge about this venom (Amorim et al, 2017).

## CONCLUSIONS

*Bothrops moojeni* venom has a rich composition that remains underexplored. As a useful tool for elucidating unknown mechanisms of different cell models, it has many components not yet studied and characterized. These may differ in function and structure from the components commonly found in the *Bothrops* family. *Bothrops moojeni* venom is rich in components poorly studied and characterized. In addition to their participation in envenoming, further studies and strategies are needed to elucidate the mechanisms of action of these different molecules, as well as their biotechnological and innovative potential. Considering that, only the molecules with higher molecular weight are often taken into consideration, new

**Table 3:** Table relating to other actions of the crude venom and its components in different models.

| Other effects | | | | | | |
|---|---|---|---|---|---|---|
| **ID uniprot** | **Molecule Name** | **Class** | **Function** | **Experimental model** | | **Reference** |
| Q6TGQ8 | L-aminoacid oxidase | L-aminoacid oxidase | Antiparasitic | *In vitro* | Leishmania sp | Tempone et al, 2014 |
| | BmooLAAO-I | L-aminoacid oxidase | Antitumor | *In vivo* | Swissmice | Stábeli et al, 2007 |
| | | | Antiparasitic | *In vitro* | *Trypanosoma cruzi* | |
| | | | Antibactericidal | *In vitro* | *Pseudomonas aeruginosa, Salmonellatyphimurium, Staphylococcus aureus.* | |
| | | | Genotoxicity | *In vitro* | Human promyelocytic leukemia cells (HL-60) | |
| | | | Plateletinhibition | *In vitro* | Plaque human | |
| G3DT18 | BmooPLA2 | Phospholipase | Antiplatelet | *In vitro* | Swissmice | Silveira et al, 2013 |
| | | | Bactericidal | *In vitro* | *Escherichia coli, Staphylococcus aureus.* | |
| | | | Cytotoxicity | *In vitro* | Human breast cancer (SK-BR-3), Acute T-cell leukemia (Jurkat), Erlichascitic tumor (EAT) | |
| | CrudeVenom | - | Genotoxicity and Cytotoxicity | *In vitro* | VERO | Novak Zobiole et al, 2015 |

technologies and methodologies are allowing the study of the low molecular weight components of these venoms, which are of utmost importance, both for elucidating the envenoming process, but also for the extensive library of new bioactive molecules that this kind of venom can offer.

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## COMPETING INTERESTS

None declared.

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